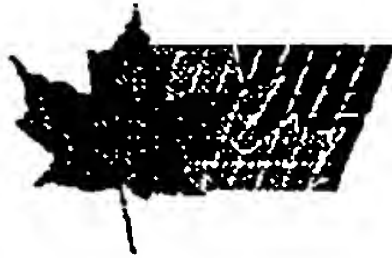


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(30) 1994/11/03 (P 44 38 861.6) DE
(54) **NOUVELLES FORMES DE PREPARATIONS DE
CYCLOSPORINES POUR ADMINISTRATION PAR VOIE
ORALE, DE COMPOSITION SIMPLE ET HAUTE
BIODISPONIBILITE, ET LEUR PROCEDE DE PRODUCTION**
(54) **NOVEL CYCLOSPORINE PREPARATION FORMS FOR ORAL
ADMINISTRATION OF SIMPLE COMPOSITION AND HIGH
BIO-AVAILABILITY, AND PROCESS FOR PRODUCING
THEM**

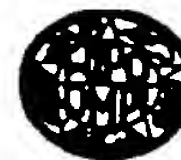
(57) L'invention concerne de nouvelles formes de préparations de cyclosporines, de composition simple et haute biodisponibilité, pour l'administration par voie orale, contenant 0,5 à 2 parties en poids d'au moins une cyclosporine amorphe, de préférence la cyclosporine A et/ou la cyclosporine G, et 6 à 9 parties en poids d'au moins un ester de polyéthylène-glycol d'acides gras hydroxy saturés C10-C22, en particulier de SOLUTOL® HS 15, ainsi que 1 à 3 parties en poids d'au moins un alcool monovalent ou multivalent, de préférence de l'éthanol et du propylène-glycol. On produit la forme médicale d'une telle préparation en faisant d'abord dissoudre la cyclosporine amorphe dans l'éthanol puis en ajoutant, en maintenant la solution sous agitation, le polypropylène-glycol et le SOLUTOL® jusqu'à obtention d'une solution claire et visqueuse, laquelle est, enfin, conditionnée de manière connue en soi sous forme de solution buvable ou de capsules.

(57) The invention relates to novel preparation forms of cyclosporine of simple composition and high bio-availability for oral administration, containing 0.5 to 2 parts by weight (p/wt) of one or more amorphous cyclosporine(s), preferably cyclosporine A and/or cyclosporine G and 6 to 9 p/wt of one or more polyethylene glycol ester(s) of saturated C10-C22 hydroxy fatty acids, especially SOLUTOL® HS 15, and 1-3 p/wt of one or more monovalent or multivalent alcohols, preferably ethanol and propylene glycol. The medical form is produced by first dissolving the amorphous cyclosporine in ethanol and adding under agitation propylene glycol and SOLUTOL® until a clear, viscous solution is obtained, which is packed as a drinking solution or capsules in the prior art manner.



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PCT WELTORGANISATION FÜR GEISTIGES EIGENTUM
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(21) Internationales Aktenzeichen: PCT/DE95/00951 (22) Internationales Anmeldedatum: 19. Juli 1995 (19.07.95) (30) Prioritätsdaten: P 44 38 861.6 3. November 1994 (03.11.94) DE (71) Anmelder (für alle Bestimmungsstaaten ausser US): ARZNEIMITTELWERK DRESDEN GMBH [DE/DE]; Fachbereich Patente, Postfach 01 01 31/01 01 32, D-01435 Radebeul (DE). (72) Erfinder; und (75) Erfinder/Anmelder (nur für US): OLBRICH, Matthias [DE/DE]; Zillerstrasse 12, D-01445 Radebeul (DE). PÖTTER, Heinrich [DE/DE]; Finstere Gasse 14, D-01445 Radebeul (DE).	(81) Bestimmungsstaaten: AU, BG, BR, BY, CA, CN, CZ, EE, FI, HU, JP, KR, KZ, LT, LV, MX, NO, PL, RO, RU, SK, UA, US, UZ, europäisches Patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Veröffentlicht <i>Mit internationalem Recherchenbericht.</i>	

(54) Title: **NOVEL CYCLOSPORINE PREPARATION FORMS FOR ORAL ADMINISTRATION OF SIMPLE COMPOSITION AND HIGH BIO-AVAILABILITY, AND PROCESS FOR PRODUCING THEM**

(54) Bezeichnung: **NEUE ZUBEREITUNGSFORMEN DES CYCLOSPORINS ZUR ORALEN APPLIKATION MIT EINFACHER ZUSAMMENSETZUNG UND HOHER BIOVERFÜGBARKEIT UND VERFAHREN ZU DEREN HERSTELLUNG**

(57) Abstract

The invention relates to novel preparation forms of cyclosporine of simple composition and high bio-availability for oral administration, containing 0.5 to 2 parts by weight (p/wt) of one or more amorphous cyclosporine(s), preferably cyclosporine A and/or cyclosporine G and 6 to 9 p/wt of one or more polyethylene glycol ester(s) of saturated C10-C22 hydroxy fatty acids, especially SOLUTOL® HS 15, and 1-3 p/wt of one or more monovalent or multivalent alcohols, preferably ethanol and propylene glycol. The medical form is produced by first dissolving the amorphous cyclosporine in ethanol and adding under agitation propylene glycol and SOLUTOL® until a clear, viscous solution is obtained, which is packed as a drinking solution or capsules in the prior art manner.

(57) Zusammenfassung

Die Erfindung betrifft neue Zubereitungsformen des Cyclosporins mit einfacher Zusammensetzung und hoher Bioverfügbarkeit zur oralen Applikation, die 0,5 bis 2 Gewichtsteile von einem oder mehreren amorphen Cyclosporin(en) bevorzugt Cyclosporin A und/oder Cyclosporin G enthalten sowie 6 bis 9 Gewichtsteile eines oder mehrerer Polyethylenglykolester von gesättigten C10-C22 Hydroxyfettsäuren insbesondere SOLUTOL® HS 15 sowie 1-3 Gewichtsteile ein oder mehrerer ein- oder mehrwertige Alkohole, bevorzugt Ethanol und Propylenglykol. Die Herstellung der Arzneiform erfolgt dadurch, daß zunächst das amorphe Cyclosporin in Ethanol gelöst wird und unter Rühren Propylenglykol und SOLUTOL® zugefügt werden bis eine klare, viskose Lösung entsteht, die in an sich bekannter Weise als Trinklösung oder Kapseln abgefüllt wird.

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**Novel Cyclosporine Preparation Forms for Oral Administration,
Having a Simple Composition and High Bioavailability, and
Process for Producing Same**

The invention concerns cyclosporine, in particular liquid preparation forms containing cyclosporine A, for oral administration.

Cyclosporines are neutral cyclic peptides which are produced in a microbic manner. The most important representative of the cyclosporines is cyclosporine A which is used in transplant medicine for suppressing organ rejection and in bone marrow transplants.

Cyclosporine A, its microbiological production as well as its isolation and cleaning until an amorphous, colorless powder is obtained is known from DE-PS 24 55 859.

Cyclosporine A is also increasingly used in the treatment of autoimmune diseases, such as psoriasis, uveitis, nephrotic syndrome and other diseases.

Antiinflammatory and antiparasitic properties are described for cyclosporines.

Due to the hydrophobic character of cyclosporine, it is difficult to produce pharmaceutical preparations which result in a high bioavailability of the active substance. In particular, the known administration forms exhibit a very high inter and intraindividual variability of the pharmacokinetic .. parameters. With the same dosage, the cyclosporine blood level varies from patient to patient by up to 50 %. Even with one and the same patient, the resorption fluctuates

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considerably. However, immunosuppressive therapy is dependent on a very narrow therapeutic window between dosis-dependent side effects and rejection of the transplanted organ.

In particular, bad bioavailabilities can be traced back to the bad solubility of the cyclosporine when mixing the cyclosporines in administration forms with water.

Thus, there have been a great many attempts to solve these galenic problems.

As a result, known, commercially available administration forms use complicated systems consisting of lipophilic and hydrophilic solvents as well as dissolving intermediary detergents with which cyclosporines are dissolved and are to be maintained in the dissolved form in aqueous systems. They consist of at least 4 components, namely active substances, vegetable oil, ethanol and a surfactant.

The use of oil and ethanol as a carrier medium in association with Co solvents is known from US Patent 4,388,307. According to this patent, conventional drinking solutions of cyclosporine contain olive oil, ethanol and as a surface-active substance Labrafil®. However, this method for preparing medicines results in problems. Oils and surface-active carrier substances often have an unpleasant smell and/or taste. Moreover, oils with unsaturated fatty acids tend to become rancid.

Secondly, a relatively high ethanol content is required in prescriptions with oils. However, this high ethanol content results in difficulties when administering the preparations to children and also involves storage problems.

When filling in capsules, to protect against evaporation, an

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increased expenditure is required during preparation by packing in aluminum blisters.

New administration forms according to the patent GB 2,222,770 include solution methods by producing microemulsions. These systems consist of 4 to 6 components which form a complicated system comprised of an active substance, a lipophilic, hydrophilic phase and a surface-active substance. Systems of this type contain an increased risk of a cross reaction as well as the risk that the patient cannot tolerate one of the substances used.

From DE-PS 39 24 207, a process for producing perorally administrable stable aqueous injection solutions is known for intravenous administration, according to which

- a) 1 part by weight of cyclosporine
- b) 8 - 13 parts by weight of one or more monoesters of a saturated hydroxy fatty acid or acids with polyethylene glycol and
- c) 1 - 3 parts by weight of one or more of monovalent and/or multivalent alcohols are mixed.

Orally administrable forms of medicines are not produced and studied in this patent. If attempts are made to dilute these prescriptions with water, this results in the precipitation of cyclosporine and thus to a considerable reduction in bioavailability.

All commercially available administration forms contain oily, lipophilic components (corn oil, core oil, corn oil mono-di-tri-glycerides) and one or more detergents as well as monovalent or multivalent alcohols.

It can be seen in DE-OS 38 43 054 that orthorhombic

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crystalline forms such as CY-A/X-II and, above all, CY-A/X-III are especially suitable for producing galenic forms. These formulations should contain cyclosporine in a stable and finely reduced form and/or have an improved stability or exhibit more advantageous releasing characteristics. Preferably, these forms are applied in a topically dermal or topically ophthalmic manner. The described manufacturing process for the solvate-free orthorhombic crystalline form using ultrasound is difficult to carry out on a technical scale.

Similarly, it is shown that cyclosporine in an amorphous form is less suitable for the production of administration forms.

According to the invention, the aforementioned problems were solved thereby that it was surprisingly found that, in administration forms of cyclosporine for oral administration with a simple composition and high bioavailability in the form of a drinking solution or capsules, containing:

- a) 0.5 to 2, preferably 1 part by weight, of one or more amorphous cyclosporine(s) as active substance
- b) 6 to 9, preferably 7.5 parts by weight, of one or more polyethylene glycol monoester of saturated C10 to C22 hydroxy fatty acids, preferably SOLUTOL® HS15
- c) 1 - 3, preferably 2 parts by weight of one or more monovalent or multivalent alcohols as Co solvent, preferably ethanol and propylene glycol, substantially increases the solubility of the cyclosporine(s), in particular in dilutions with water, while maintaining these special quantitative ratios.

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This was not generally assumed since comparable administration forms only use polyethylene glycol esters of fatty acids as additional dissolving intermediary between a hydrophobic and hydrophilic phase.

Thus, it was all the more surprising that a prescription of this type showed a bioequivalence vis-à-vis commercial products (see above).

In particular, it could not be foreseen that such a simple prescription could attain such a high bioavailability without lipophilic components.

Furthermore, it was found that it was just the use of amorphous cyclosporine in an oral administration form results in especially good solution properties in recipes with a cyclosporine content of > 5 %, which are also preserved as a stable, clear solution in dilutions with water.

Thus, oral administration forms are the object of the invention which, as a drinking solution or packed in capsules, contain the following components in the following quantitative ratios:

a) 0.5 - 2 parts by weight, preferably 1 part by weight, of one or more cyclosporines, in particular cyclosporine A or G, which is used in an amorphous form

b) 6 - 9 parts by weight, preferably 7.5 parts by weight, of one or more polyethylene glycol monoesters with saturated C10 to C22 of hydroxy fatty acid components, bound in the molecule, in particular SOLUTEL® HS 15

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c) 1 to 3 parts by weight, preferably 2 parts by weight, of one or more monovalent or multivalent alcohols as Co solvent, preferably ethanol and propylene glycol.

In the manufacturing process, also according to the invention, it should be noted that the quantitative ratios are maintained and that the cyclosporine, while being continuously stirred at room temperature, is first completely dissolved in ethanol and that, subsequently, also while being stirred continuously and also at room temperature, propylene glycol and Solutol® HS 15 is added. The solutions produced according to this process contain 100 mg/ml active substance.

The product packaged in the form of a drinking solution or capsules is prepared in a known manner, e.g. in capsules at 100 mg each, 50 mg or 25 mg active substance.

The production of the composition according to the invention is described in greater detail in the following examples:

Example 1

100 g amorphous cyclosporine A are dissolved in 127 ml ethanol while being stirred at room temperature. 96 ml propylene glycol are subsequently added under continuous stirring at room temperature. After the cyclosporine A has been clearly dissolved, 750 g Solutol® HS 15 are added under continuous stirring. A clear, viscous solution results with a content of 100 mg/ml cyclosporine A.

Example 2

A cyclosporine A solution, produced according to Example 1, is diluted with water in the ratio 1 : 40. The resultant solution remains clear and stable over a period of several months.

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Patent Claims

1. Novel cyclosporine preparation forms for oral administration, having a simple composition and a high bioavailability, in the form of a drinking solution or capsules, containing:

- a) 0.5 to 2, preferably 1 part by weight, of one or more amorphous cyclosporine(s) as active substance
- b) 6 to 9, preferably 7.5 parts by weight, of one or more polyethylene glycol monoesters of saturated C10 - C22 hydroxy fatty acids, preferably SOLUTOL® HS15
- c) 1 - 3, preferably 2 parts by weight of one or more monovalent or multivalent alcohols as Co solvent, preferably ethanol and propylene glycol

as well as the production thereof.

2. An administration form according to claim 1, wherein cyclosporine A or cyclosporine G in an amorphous form are used as active substance.

3. Process for the production of novel cyclosporine preparation forms for oral administration, having a simple composition and high bioavailability, in the form of a drinking solution or capsules according to claim 1 and 2, in which, first of all, while being stirred at room temperature,

- a) 100g amorphous cyclosporine, in particular cyclosporine A, are dissolved in 127 ml ethanol
- b) also while being stirred and at room temperature, 96 ml propylene glycol are added and, finally, also

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- while being stirred at room temperature,
- c) 750 g Solutol HS 15 are added, whereby a clear, viscous solution of the cyclosporine A is produced which is packaged as a drinking solution or capsules in a known manner.